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| 10/556,224 | 09/27/2006 | Martin Hendrix | 01-2116 | 3652 |

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| EXAMINER | |
|---|---|
| MOORE, SUSANNA | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

| NOTIFICATION DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/556,224 | HENDRIX ET AL. | |
| | Examiner | Art Unit | |
| | SUSANNA MOORE | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,9,13 and 14* is/are pending in the application.

4a) Of the above claim(s) *7,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

Applicant's arguments, see Remarks, filed 2/20/2009, with respect to Office Action mailed 10/20/2008 have been fully considered. Some of the rejections have been withdrawn, others have been maintained, and some are new rejections as a result of Applicant's amendments. Thus, this is a Final Office Action. In summary, claims 1-6, 9, 13 and 14 are currently pending. Claims 7, 13 and 14 are currently withdrawn.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on 4/23/2009 was filed after the mailing date of the Non-final Office Action on 10/20/2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Most of the references were considered on a previous IDS, dated 7/21/2008. The reference CH 396925 was not considered because the reference was not found in the file.

### *Specification*

The objection of the title of the invention is **withdrawn** based on the amendments.

The disclosure is objected to because of the following informalities:

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

**Arrangement of the Specification**

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The above objection is **maintained** since Applicant did not address this issue.

The objection to the abstract of the disclosure is **withdrawn** based on the amendments.

***Information Disclosure Statement***

The information disclosure statements (IDSs) submitted on 7/21/2008, 9/27/06 and 11/9/2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

***Claim Objections***

The objection of claims 7, 13 and 14, drawn to an invention nonelected without traverse in the paper of 7/21/2008 is **withdrawn** based on the amendments.

The objection to claims 2-6 and 9 because of the following informalities: the term "Claim" should not be capitalized is **withdrawn** based on the amendments.

The objection to claims 5 and 6 because of the following informalities: the preamble states, "A compound Claim 1," which is not grammatically correct is **withdrawn** based on the amendments.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salts of a compound of

formula (I) does not reasonably provide enablement for a solvate of compound of formula (I) of claim 1. The specification does not provide sufficient guidance nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

***The nature of the invention***

The nature of the invention is a compound of the formula in claim 1, or a pharmaceutically acceptable salt of said compound. The only teaching of solvates of the compounds of formula of claim 1 in the specification is the definition of the term solvates, generally, on page 5.

***The state of the prior art and predictability or lack thereof in the art***

It is the state of the prior art that the term "solvate" found in the claims is defined as a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates and hence generalizations cannot be made for a series of related compound (See Vippagunta, et al.)

The scope of "solvate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active in vivo. Solvates and hydrates cannot always be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

***The amount of direction or guidance present and the presence or absence of working examples***

There is no direction or guidance present in the specification or working examples present in the specification that define or relate to specific solvates intended as part of the compounds being included in the elected invention.

***The breadth of the claims***

The breadth of the claims is a compound of formula (I) of claim 1 or a pharmaceutically acceptable salt or solvate thereof.

***The quantity of experimentation needed and the level of the skill in the art***

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents without any direction as to what compounds form solvates with which solvents.

***The level of skill in the art*** **is high without showing or guidance as to how to make** solvates of a conjugate of claim 1 it would require undue experimentation to figure out the solvents, temperatures and reaction times that would provide solvates of the above compounds.

To overcome this objection, Applicant should submit an amendment deleting the term "solvates."

Applicant traverses the above rejection by stating, "The position taken in the Office action is that formation of solvates requires undue experimentation and is unpredictable. Applicants believe that this conclusion was arrived at because the wrong question is being considered. The conclusion in the Office action appears to be based on the question of whether it is routine or predictable - without conducting any experimentation - to determine whether a specific solvent will form a solvate with a specific compound and what the nature of such solvate would be. The correct question should be: Can one of ordinary skill in the art conduct routine experimentation to provide solvates of the claimed compounds which would be useful for carrying out the invention and can one of ordinary skill in the art routinely determine the nature

of any such solvates? Applicants submit that this latter question is the proper one because the law is clear that adequate enablement can be provided from the knowledge available in the art and can be provided from one of ordinary skill in the art conducting routine experimentation."

Applicant is not correct. **The Wands factors as a whole must be taken into consideration when addressing the enablement issue**. Furthermore, the art of forming solvates is unpredictable, as Applicant has noted, and can be further illustrated by the ritonivir case (Abbott Laboratories), see the Rowe et. al. (DDT, 2001, 6(8), 2001, pages 395-396). Rowe states, "Polymorphs can seemingly appear and disappear for no apparent reason and new ones can appear when least expected. The occurrence of new polymorphs, in particular, can have disastrous consequences, not least the disruption of production. A celebrated example of this is the protease inhibitor, ritonavir…; the unexpected appearance of a new crystal form of this drug that had different dissolution characteristics resulted in a shortage of the capsule formulation during the summer of 1998." See page 395, far right-hand column, lines 1-9. Thus, the example illustrates the unpredictability of solvates by showing one of ordinary skill in the art could not routinely predict solvate formation.

Applicant goes on to remark, "Vippagunta may support the notion that one of ordinary skill in the art cannot accurately predict - beforehand - whether a particular compound will form a solvate with a particular solvent or what the nature of the resulting solvate would be. But, as discussed above, this is not the proper inquiry. The article supports that only routine experimentation by one of ordinary skill in the art is needed to identify, prepare and characterize suitable solvates of a given compound. For example, Vippagunta on page 15, top of first column, states:…"

Vippagunta also states, "The mere presence of water in a system is not a sufficient reason to expect hydrate formation, because some compounds, though they are soluble in water, do not form hydrates." See page 15, left hand colum, first full paragraph.

Applicant has also stated, "… one third of the pharmaceutically active substances are capable of forming crystalline hydrates…" but this does not mean that one third of pharmaceutically active substances actually do form crystalline hydrates. Another recited quote by Applicant states, "Many drugs exist in crystalline solid state..." which "can exist in the form of polymorphs," however just because a drug can exist in a solid state does not mean the crystalline form is a polymorph or solvate. Applicant also cites known analytical techniques used in solid state chemistry which are also used to characterize solvates.

Applicant has cited Hilfiker et. al. (J.Therm.Anal.Cal., vol. 73 (2003), pp. 429-440), which reflects the state of the art contemporaneous with the time of applicants' invention. The article (page 430) recognizes that it was known to perform polymorphism screening using high-throughput screening techniques which were available to perform such steps more quickly with less resources. The reference utilizes only carbamazepine (CBZ) as a model substance, not a plethora of substances with different properties and functional groups.

In *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well. One skilled in the art knows that solvates are prepared by exposing the compound to solvent (e.g. by preparing in the presence of solvent) and then isolating the solid. If the compound inherently forms solvates, then one will get a solvate; if not, one will not. That is, some compounds form solvates; some do not. These

compounds, judging by the evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound, which does not naturally form one, to form a solvate. The specification does not even seem to be aware of the problem. The remarks do not state how to do this, nor does the examiner know of any such technique.

One skilled in the art knows that hydrates (and other solvates; "hydrates" are the type of solvates where the solvent is water) are prepared by exposing the compound to water (e.g. by preparing in the presence of water) and then isolating the solid. If the compound inherently forms hydrates (or solvates), then one will get a hydrate; if not, one will not.

With regard to *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well. There are dozens of examples reported; not one of them produced a solvate.

Applicant goes on to recite, "Further, it would be routine in the art to determine whether or not solvates are possible for any specific compound. While predicting what solvates could be formed before doing any experimentation may be difficult, the formation of solvates is common with pharmaceutically active ingredients and methods of providing and characterizing them are well-known and widely applied routinely."

Applicant has provides limited direction on page 5 of how one might go about making/using solvates of the claimed compounds. The issue is not the ability of some compounds to form solvates, but which ones, what the composition of those solvates, and the structure of those solvates. It is not the Examiner's position that no solvates will form from

Applicants' compounds. Rather it is totally unpredictable which compounds will form solvates, what will be the elemental composition of those solvates, and that the structure of those solvates are beyond the ability of present chemical science to predict. Further evidence of the lack of predictability in the solvate forming arts, cited for rebuttal, is provided by Vippagunta (Advanced Drug Delivery Reviews), who states on page 18, section 3.4, "[p]redicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult". "[N]o computer programs are currently available for predicting the crystal structures of hydrates and solvates". Reconsideration of all the evidence related to each of these factors, and based on the evidence as a whole, the specification, at the time the application was filed, would not have taught one skilled in the art how make the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510. Thus, undue experimentation will be required to determine if any particular claimed compound is, in fact, a solvate or how to make and what the structure will be of any claimed solvate.

Applicant cites reference to several US patents, Us 7351841, 7321059, 7320995, 7432272 and 7345806 in the state of the art section of the rebuttal (page 17). However, each case is taken on its own merits, and as such, the Examiner will not comment on any other patent.

Thus, taken as a whole, and for those reasons cited above, the rejection is **maintained**.

### *Claim Rejections - 35 USC § 102*

The rejection of claims 1-6 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Linker et. al. (DE 10219435) is **withdrawn**.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et. al. (J. Org. Chem, 1958, (23) 191-200).

The instant Application claims compounds of formula (I), wherein $R^1$= ethyl and $R^2$= 4-methylphenyl.

The reference teaches compounds of formula (I), wherein $R^1$= ethyl and $R^2$= phenyl. See page 195, table II, the 17th specie listed from top to bottom. Also note, the compounds were recrystallized in ethanol and water, pharmaceutically acceptable carriers.

The only difference between the instant Application and the reference is the substituent at $R^2$, a phenyl versus Applicant's 4-methylphenyl. The reference teaches guideposts with 4-methylphenyl, see the 19th specie listed in table II. Furthermore, since a methyl group is considered a homolog of hydrogen these compounds are considered equivalent. The MPEP 2144.09 states "Compounds which are… homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Also, note *In re Magerlein*, 202 USPQ 473; *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr,* 137 USPQ 548.

Additionally, the instant Application claims compounds of formula (I), wherein $R^1$= ethyl and $R^2$= 4-methylphenyl.

The reference teaches compounds of formula (I), wherein $R^1$= methyl and $R^2$= 4-methylphenyl. See page 195, table II, the 19th specie listed from top to bottom. Also note, the compounds were recrystallized in ethanol and water, pharmaceutically acceptable carriers.

The only difference between the instant Application and the reference is the substituent at $R^1$, a methyl versus Applicant's ethyl. The reference teaches guideposts with ethyl, see the 17th specie listed in table II. Furthermore, the MPEP 2144.09 states "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) … are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Applicant traverses the above rejection by stating, "Cheng provides only a brief and abstract discussion of possible activity of compounds in the paragraph at page 193, bottom left-side column. This discussion does not set forth any actual utility for the compounds discussed there. In any event, it should be clear that - even if this discussion did adequately describe a utility - it does not pertain to the compounds disclosed in Cheng which are most similar to the claimed compounds. There is no basis to tie this discussion in Cheng with the 6-alkyl-4-hydroxy-pyrazolo-[3,4- d]pyrimidine compounds disclosed in Cheng's formula VI and Table II. To the contrary, the only compound which Cheng identifies as having some activity (i.e., for inhibiting Neurospora crassa) is a compound having a 4-amino group like those described in Cheng's formula XV and Table III."

This is not found persuasive. Applicant agrees that the compounds outlined above are adjacent homologues, see page 21, third full paragraph, lines 4-5. The 4-hydroxypyrazolo[3,4-d]pyrimidines are **not** intermediates, as Applicant noted in the remarks. See Skipper et. al. (Cancer Research, 1957, 17, pages 579-596), which is footnote 10 at the bottom of page 193 of

Cheng et. al., which clearly indicates the 4-hydroxypyrazolo[3,4-d]pyrimidines were tested, see page 587, compound 73.

Thus, the rejection is **maintained**.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSANNA MOORE whose telephone number is (571)272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/
Examiner, Art Unit 1624

**/James O. Wilson/**
**Supervisory Patent Examiner, Art Unit 1624**